CLAIMS

What is claimed is:

1. A method of detecting autoimmune disease in a mammal, comprising

a) providing a biological sample from a mammal; and

b) detecting proteasome activity, wherein a reduction in said proteasome activity from a basal state is indicative of autoimmune disease.

2. The method according to claim 1, wherein said biological sample comprises protein.

3. The method according to claim 1, wherein a said reduction in said proteasome activity is detected.

4. The method according to claim 1, wherein said reduction in said proteasome activity comprises a reduction of proteolytic processing of NFκB, p105, p100, IκB, or a subunit thereof.

5. The method according to claim 1, wherein said mammal is a human.

6. The method according to claim 5, wherein said autoimmune disease is an HLA class II-linked disease.

7. The method according to claim 5, wherein said autoimmune disease is selected from the group that includes diabetes, rheumatoid arthritis, multiple sclerosis, lupus erythematosis, myasthenia gravis, scleroderma, Crohn's disease, ulcerative colitis, Hashimoto's disease, Graves' disease, Sjögren's syndrome, polyendocrine failure, vitiligo, peripheral neuropathy, graft-versus-host disease, autoimmune polyglandular syndrome type I, acute glomerulonephritis, Addison's disease, adult-onset idiopathic hypoparathyroidism (AOIH), alopecia totalis, amyotrophic lateral sclerosis, ankylosing spondylitis, autoimmune aplastic anemia, autoimmune hemolytic anemia, Behcet's disease, Celiac disease, chronic active hepatitis, CREST syndrome, dermatomyositis, dilated cardiomyopathy, eosinophilia-myalgia syndrome, epidermolisis bullosa acquisita (EBA), giant cell arteritis, Goodpasture's syndrome, Guillain-Barré syndrome, hemochromatosis, Henoch-Schönlein purpura, idiopathic IgA nephropathy, insulin-dependent diabetes mellitus (IDDM), juvenile rheumatoid arthritis, Lambert-Eaton syndrome, linear IgA

dermatosis, myocarditis, narcolepsy, necrotizing vasculitis, neonatal lupus syndrome (NLE), nephrotic syndrome, pemphigoid, pemphigus, polymyositis, primary sclerosing cholangitis, psoriasis, rapidly-progressive glomerulonephritis (RPGN), Reiter's syndrome, stiff-man syndrome and thyroiditis.

8. A method of detecting autoimmune disease in a mammal, comprising

a) providing a biological sample from a mammal; and

b) detecting protein ubiquitination, wherein a reduction in said protein ubiquitination from a basal state is indicative of autoimmune disease.

9. The method according to claim 8, wherein said biological sample comprises protein.

10. The method according to claim 8, wherein a said reduction in said protein ubiquitination is detected for a protein.

11. The method according to claim 8, wherein said mammal is a human.

12. The method according to claim 11, wherein said autoimmune disease is an HLA class II-linked disease.

13. The method according to claim 11, wherein said autoimmune disease is selected from the group that includes diabetes, rheumatoid arthritis, multiple sclerosis, lupus erythematosis, myasthenia gravis, scleroderma, Crohn's disease, ulcerative colitis, Hashimoto's disease, Graves' disease, Sjögren's syndrome, polyendocrine failure, vitiligo, peripheral neuropathy, graft-versus-host disease, autoimmune polyglandular syndrome type I, acute glomerulonephritis, Addison's disease, adult-onset idiopathic hypoparathyroidism (AOIH), alopecia totalis, amyotrophic lateral sclerosis, ankylosing spondylitis, autoimmune aplastic anemia, autoimmune hemolytic anemia, Behcet's disease, Celiac disease, chronic active hepatitis, CREST syndrome, dermatomyositis, dilated cardiomyopathy, eosinophilia-myalgia syndrome, epidermolisis bullosa acquisita (EBA), giant cell arteritis, Goodpasture's syndrome, Guillain-Barré syndrome, hemochromatosis, Henoch-Schönlein purpura, idiopathic IgA nephropathy, insulin-dependent diabetes mellitus (IDDM), juvenile rheumatoid arthritis, Lambert-Eaton syndrome, linear IgA dermatosis, myocarditis, narcolepsy, necrotizing vasculitis, neonatal lupus syndrome (NLE),

nephrotic syndrome, pemphigoid, pemphigus, polymyositis, primary sclerosing cholangitis, psoriasis, rapidly-progressive glomerulonephritis (RPGN), Reiter's syndrome, stiff-man syndrome and thyroiditis.

14. A method of detecting autoimmune disease in a mammal, comprising

a) providing a biological sample from a mammal; and

b) detecting protein phosphorylation, wherein a reduction in said protein phosphorylation from a basal state is indicative of autoimmune disease.

15. The method according to claim 14, wherein said biological sample comprises protein.

16. The method according to claim 14, wherein a said reduction in said protein phosphorylation is detected.

17. The method according to claim 14, wherein said mammal is a human.

18. The method according to claim 17, wherein said autoimmune disease is an HLA class II-linked disease.

19. The method according to claim 17, wherein said autoimmune disease is selected from the group that includes diabetes, rheumatoid arthritis, multiple sclerosis, lupus erythematosis, myasthenia gravis, scleroderma, Crohn's disease, ulcerative colitis, Hashimoto's disease, Graves' disease, Sjögren's syndrome, polyendocrine failure, vitiligo, peripheral neuropathy, graft-versus-host disease, autoimmune polyglandular syndrome type I, acute glomerulonephritis, Addison's disease, adult-onset idiopathic hypoparathyroidism (AOIH), alopecia totalis, amyotrophic lateral sclerosis, ankylosing spondylitis, autoimmune aplastic anemia, autoimmune hemolytic anemia, Behcet's disease, Celiac disease, chronic active hepatitis, CREST syndrome, dermatomyositis, dilated cardiomyopathy, eosinophilia-myalgia syndrome, epidermolisis bullosa acquisita (EBA), giant cell arteritis, Goodpasture's syndrome, Guillain-Barré syndrome, hemochromatosis, Henoch-Schönlein purpura, idiopathic IgA nephropathy, insulin-dependent diabetes mellitus (IDDM), juvenile rheumatoid arthritis, Lambert-Eaton syndrome, linear IgA dermatosis, myocarditis, narcolepsy, necrotizing vasculitis, neonatal lupus syndrome (NLE), nephrotic syndrome, pemphigoid, pemphigus, polymyositis, primary sclerosing cholangitis,

psoriasis, rapidly-progressive glomerulonephritis (RPGN), Reiter's syndrome, stiff-man syndrome and thyroiditis.

20. A method of detecting autoimmune disease in a mammal, comprising

a) providing a biological sample from a mammal; and

b) detecting NFκB activity, wherein a reduction in said NFκB activity from a basal state is indicative of autoimmune disease.

21. The method according to claim 20, wherein said biological sample comprises protein.

22. The method according to claim 20, wherein said biological sample comprises a nucleic acid.

23. The method of claim 20, wherein a said reduction in said NFκB activity is detected.

24. The method according to claim 20, wherein said mammal is human.

25. The method according to claim 24, wherein said autoimmune disease is an HLA class II-linked disease.

26. The method according to claim 24, wherein said autoimmune disease is selected from the group that includes diabetes, rheumatoid arthritis, multiple sclerosis, lupus erythematosis, myasthenia gravis, scleroderma, Crohn's disease, ulcerative colitis, Hashimoto's disease, Graves' disease, Sjögren's syndrome, polyendocrine failure, vitiligo, peripheral neuropathy, graft-versus-host disease, autoimmune polyglandular syndrome type I, acute glomerulonephritis, Addison's disease, adult-onset idiopathic hypoparathyroidism (AOIH), alopecia totalis, amyotrophic lateral sclerosis, ankylosing spondylitis, autoimmune aplastic anemia, autoimmune hemolytic anemia, Behcet's disease, Celiac disease, chronic active hepatitis, CREST syndrome, dermatomyositis, dilated cardiomyopathy, eosinophilia-myalgia syndrome, epidermolisis bullosa acquisita (EBA), giant cell arteritis, Goodpasture's syndrome, Guillain-Barré syndrome, hemochromatosis, Henoch-Schönlein purpura, idiopathic IgA nephropathy, insulin-dependent diabetes mellitus (IDDM), juvenile rheumatoid arthritis, Lambert-Eaton syndrome, linear IgA dermatosis, myocarditis, narcolepsy, necrotizing vasculitis, neonatal lupus syndrome (NLE),

nephrotic syndrome, pemphigoid, pemphigus, polymyositis, primary sclerosing cholangitis, psoriasis, rapidly-progressive glomerulonephritis (RPGN), Reiter's syndrome, stiff-man syndrome and thyroiditis.

27. A method of detecting autoimmune disease in a mammal, comprising

a) providing a biological sample from a mammal; and

b) detecting cell survival or growth, wherein cell death in a tissue that is a suspected target of said autoimmune disease is indicative of autoimmune disease.

28. The method according to claim 27, wherein said sample is obtained from said mammal at an early stage in said disease prior to the formation of autoantibodies against said tissue.

29. The method according to claim 28, wherein cell death is detected in a said tissue that is a said suspected target of autoimmune disease prior to or early in the formation of said autoantibodies.

30. The method according to claim 27, wherein said biological sample comprises cells of said tissue that is a said suspected target of autoimmune disease.

31. The method according to claim 27, wherein said mammal is a human.

32. The method according to claim 31, wherein said autoimmune disease is an HLA class II-linked disease.

33. The method according to claim 31, wherein said autoimmune disease is selected from the group that includes diabetes, rheumatoid arthritis, multiple sclerosis, lupus erythematosis, myasthenia gravis, scleroderma, Crohn's disease, ulcerative colitis, Hashimoto's disease, Graves' disease, Sjögren's syndrome, polyendocrine failure, vitiligo, peripheral neuropathy, graft-versus-host disease, autoimmune polyglandular syndrome type I, acute glomerulonephritis, Addison's disease, adult-onset idiopathic hypoparathyroidism (AOIH), alopecia totalis, amyotrophic lateral sclerosis, ankylosing spondylitis, autoimmune aplastic anemia, autoimmune hemolytic anemia, Behcet's disease, Celiac disease, chronic active hepatitis, CREST syndrome, dermatomyositis, dilated cardiomyopathy, eosinophilia-myalgia syndrome, epidermolisis bullosa

acquisita (EBA), giant cell arteritis, Goodpasture's syndrome, Guillain-Barré syndrome, hemochromatosis, Henoch-Schönlein purpura, idiopathic IgA nephropathy, insulin-dependent diabetes mellitus (IDDM), juvenile rheumatoid arthritis, Lambert-Eaton syndrome, linear IgA dermatosis, myocarditis, narcolepsy, necrotizing vasculitis, neonatal lupus syndrome (NLE), nephrotic syndrome, pemphigoid, pemphigus, polymyositis, primary sclerosing cholangitis, psoriasis, rapidly-progressive glomerulonephritis (RPGN), Reiter's syndrome, stiff-man syndrome and thyroiditis.

34. A method of treating an autoimmune disease in a mammal, comprising administering to a mammal suspected of suffering from said autoimmune disease an agent which restores protein ubiquitinating enzyme function in an amount and for a time sufficient to result in normal protein ubiquitination in said mammal.

35. The method according to claim 34, wherein said agent is selected from the group that consists of a protein and a nucleic acid that encodes said protein.

36. The method according to claim 35, wherein said protein is selected from the group that includes a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2) and ubiquitin-ligases (E3).

37. The method according to claim 34, wherein said agent is a nucleic acid which encodes an antisense RNA or a ribozyme.

38. The method according to claim 34, wherein said mammal is a human.

39. The method according to claim 38, wherein said autoimmune disease is an HLA class II-linked disease.

40. The method according to claim 38, wherein said autoimmune disease is selected from the group that includes diabetes, rheumatoid arthritis, multiple sclerosis, lupus erythematosis, myasthenia gravis, scleroderma, Crohn's disease, ulcerative colitis, Hashimoto's disease, Graves' disease, Sjögren's syndrome, polyendocrine failure, vitiligo, peripheral neuropathy, graft-versus-host disease, autoimmune polyglandular syndrome type I, acute glomerulonephritis, Addison's disease, adult-onset idiopathic hypoparathyroidism (AOIH), alopecia totalis,

amyotrophic lateral sclerosis, ankylosing spondylitis, autoimmune aplastic anemia, autoimmune hemolytic anemia, Behcet's disease, Celiac disease, chronic active hepatitis, CREST syndrome, dermatomyositis, dilated cardiomyopathy, eosinophilia-myalgia syndrome, epidermolisis bullosa acquisita (EBA), giant cell arteritis, Goodpasture's syndrome, Guillain-Barré syndrome, hemochromatosis, Henoch-Schönlein purpura, idiopathic IgA nephropathy, insulin-dependent diabetes mellitus (IDDM), juvenile rheumatoid arthritis, Lambert-Eaton syndrome, linear IgA dermatosis, myocarditis, narcolepsy, necrotizing vasculitis, neonatal lupus syndrome (NLE), nephrotic syndrome, pemphigoid, pemphigus, polymyositis, primary sclerosing cholangitis, psoriasis, rapidly-progressive glomerulonephritis (RPGN), Reiter's syndrome, stiff-man syndrome and thyroiditis.

41. A method of restoring NFκB activity in a mammal afflicted with an autoimmune disease resulting from a reduction in NFκB activity, comprising administering to a mammal suspected of suffering from said autoimmune disease a therapeutically effective amount of agent which restores NFκB activity 50 hours to treat said disease in said mammal.

42. The method according to claim 41, wherein said agent is a protein.

43. The method according to claim 42, wherein said protein is selected from the group consisting of NFκB, NFκB p50, NFκB p52, NFκB p65, and IκB.

46. The method according to claim 41, wherein said mammal is a human.

47. The method according to claim 46, wherein said autoimmune disease is an HLA class II-linked disease.

48. The method according to claim 46, wherein said autoimmune disease is selected from the group that includes diabetes, rheumatoid arthritis, multiple sclerosis, lupus erythematosis, myasthenia gravis, scleroderma, Crohn's disease, ulcerative colitis, Hashimoto's disease, Graves' disease, Sjögren's syndrome, polyendocrine failure, vitiligo, peripheral neuropathy, graft-versus-host disease, autoimmune polyglandular syndrome type I, acute glomerulonephritis, Addison's disease, adult-onset idiopathic hypoparathyroidism (AOIH), alopecia totalis, amyotrophic lateral sclerosis, ankylosing spondylitis, autoimmune aplastic anemia, autoimmune hemolytic anemia, Behcet's disease, Celiac disease, chronic active hepatitis, CREST syndrome,

dermatomyositis, dilated cardiomyopathy, eosinophilia-myalgia syndrome, epidermolisis bullosa acquisita (EBA), giant cell arteritis, Goodpasture's syndrome, Guillain-Barré syndrome, hemochromatosis, Henoch-Schönlein purpura, idiopathic IgA nephropathy, insulin-dependent diabetes mellitus (IDDM), juvenile rheumatoid arthritis, Lambert-Eaton syndrome, linear IgA dermatosis, myocarditis, narcolepsy, necrotizing vasculitis, neonatal lupus syndrome (NLE), nephrotic syndrome, pemphigoid, pemphigus, polymyositis, primary sclerosing cholangitis, psoriasis, rapidly-progressive glomerulonephritis (RPGN), Reiter's syndrome, stiff-man syndrome and thyroiditis.

49. A method of treating an autoimmune disease in a mammal, comprising administering to a mammal suspected of suffering from said autoimmune disease resulting from a reduction in the activity of NFκB, DNA repair factor TFIIH, STAT transcription factor, ubiquitination, phosphorylation or the proteasome an agent which restores lymphocyte maturation in an amount and for a time sufficient to result in normal lymphocyte maturation in said mammal.

50. The method according to claim 49, wherein said agent is selected from the group that consists of a protein and a nucleic acid that encodes said protein.

51. The method according to claim 50, wherein said protein is selected from the group that includes apolipoprotein B100, DNA repair factor TFIIH, STAT transcription factor, a mutant- or wild-type NFκB p50, a mutant- or wild-type NFκB p65, tumor necrosis factor-α, E-selectin, I-cam, and V-cam, interleukin-2, interleukin-6, granulocyte colony-stimulating factor, interferon-β, Lmp2, Lmp7, a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2), a ubiquitin-ligase (E3), a protein kinase, a proteasome subunit and an antibody directed against one of the 240 kD and 200 kD human erythrocyte proteasome inhibitors, CF-2 and IκB.

52. The method according to claim 49, wherein said agent is selected from the group that includes a ribozyme, an antisense RNA molecule, a DNA molecule that encodes a said ribozyme and a DNA molecule that encodes a said antisense RNA molecule.

53. The method according to claim 52, wherein said ribozyme or said antisense RNA molecule is directed against one of the 240 kD and 200 kD human erythrocyte proteasome inhibitors, CF-2 and IκB.

54. The method according to claim 49, wherein said mammal is a human.

55. The method according to claim 54, wherein said autoimmune disease is an HLA class II-linked disease.

56. The method according to claim 54, wherein said autoimmune disease is selected from the group that includes diabetes, rheumatoid arthritis, multiple sclerosis, lupus erythematosis, myasthenia gravis, scleroderma, Crohn's disease, ulcerative colitis, Hashimoto's disease, Graves' disease, Sjögren's syndrome, polyendocrine failure, vitiligo, peripheral neuropathy, graft-versus-host disease, autoimmune polyglandular syndrome type I, acute glomerulonephritis, Addison's disease, adult-onset idiopathic hypoparathyroidism (AOIH), alopecia totalis, amyotrophic lateral sclerosis, ankylosing spondylitis, autoimmune aplastic anemia, autoimmune hemolytic anemia, Behcet's disease, Celiac disease, chronic active hepatitis, CREST syndrome, dermatomyositis, dilated cardiomyopathy, eosinophilia-myalgia syndrome, epidermolisis bullosa acquisita (EBA), giant cell arteritis, Goodpasture's syndrome, Guillain-Barré syndrome, hemochromatosis, Henoch-Schönlein purpura, idiopathic IgA nephropathy, insulin-dependent diabetes mellitus (IDDM), juvenile rheumatoid arthritis, Lambert-Eaton syndrome, linear IgA dermatosis, myocarditis, narcolepsy, necrotizing vasculitis, neonatal lupus syndrome (NLE), nephrotic syndrome, pemphigoid, pemphigus, polymyositis, primary sclerosing cholangitis, psoriasis, rapidly-progressive glomerulonephritis (RPGN), Reiter's syndrome, stiff-man syndrome and thyroiditis.

57. A method of treating an autoimmune disease in a mammal, comprising administering to a mammal suspected of suffering from a said autoimmune disease resulting from a reduction in the activity of NFκB, DNA repair factor TFIIH, STAT transcription factor, ubiquitination, phosphorylation or the proteasome an agent which restores the cell cycle in an amount and for a time sufficient to result in normal survival of cells of a tissue that is susceptible to a said autoimmune disease prior to the formation of autoantibodies against said cells in said mammal.

58. The method according to claim 57, wherein said agent is selected from the group that includes a protein and a nucleic acid that encodes said protein.

59. The method according to claim 58, wherein said protein is selected from the group that includes a cyclin, a cyclin-dependent kinase, apolipoprotein B100, DNA repair factor TFIIH, STAT transcription factor, a mutant- or wild-type NFκB p50, a mutant- or wild-type NFκB p65, tumor necrosis factor-α, E-selectin, I-cam, and V-cam, interleukin-2, interleukin-6, granulocyte colony-stimulating factor, interferon-β, Lmp2, Lmp7, a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2), a ubiquitin-ligase (E3), a protein kinase, a proteasome subunit and an antibody directed against one of the 240 kD and 200 kD human erythrocyte proteasome inhibitors, CF-2 and IκB.

60. The method according to claim 57, wherein said agent is selected from the group that includes a ribozyme, an antisense RNA molecule, a DNA molecule that encodes a said ribozyme and a DNA molecule that encodes a said antisense RNA molecule.

61. The method according to claim 60, wherein said ribozyme or said antisense RNA molecule is directed against one of the 240 kD and 200 kD human erythrocyte proteasome inhibitors, CF-2 and IκB.

62. The method according to claim 57, wherein said mammal is a human.

63. The method according to claim 62, wherein said autoimmune disease is an HLA class II-linked disease.

64. The method according to claim 62, wherein said autoimmune disease is selected from the group that includes diabetes, rheumatoid arthritis, multiple sclerosis, lupus erythematosis, myasthenia gravis, scleroderma, Crohn's disease, ulcerative colitis, Hashimoto's disease, Graves' disease, Sjögren's syndrome, polyendocrine failure, vitiligo, peripheral neuropathy, graft-versus-host disease, autoimmune polyglandular syndrome type I, acute glomerulonephritis, Addison's disease, adult-onset idiopathic hypoparathyroidism (AOIH), alopecia totalis, amyotrophic lateral sclerosis, ankylosing spondylitis, autoimmune aplastic anemia, autoimmune hemolytic anemia, Behcet's disease, Celiac disease, chronic active hepatitis, CREST syndrome, dermatomyositis, dilated cardiomyopathy, eosinophilia-myalgia syndrome, epidermolisis bullosa acquisita (EBA), giant cell arteritis, Goodpasture's syndrome, Guillain-Barré syndrome, hemochromatosis, Henoch-Schönlein purpura, idiopathic IgA nephropathy, insulin-dependent

diabetes mellitus (IDDM), juvenile rheumatoid arthritis, Lambert-Eaton syndrome, linear IgA dermatosis, myocarditis, narcolepsy, necrotizing vasculitis, neonatal lupus syndrome (NLE), nephrotic syndrome, pemphigoid, pemphigus, polymyositis, primary sclerosing cholangitis, psoriasis, rapidly-progressive glomerulonephritis (RPGN), Reiter's syndrome, stiff-man syndrome and thyroiditis.

65. A method for screening for a modulator of LMP2 function, comprising the steps of:

a) contacting an assay system with a candidate modulator of LMP2, wherein in said system, proteasome-mediated cleavage of a ubiquitinated protein occurs, and

b) monitoring cleavage of said ubiquitinated protein, wherein a change in said cleavage resulting from said contacting indicates that said candidate modulator is effective as a modulator of LMP2 function.